8-14-07

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427.035-DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
KATY DRIEU	:	Group: 1657
Serial No.: 10/809,617	:	
Filed: March 25, 2004	:	Examiner: Gough, Tiffany Maureen
For: USE...PREPARING A MEDICINE	:	

Hedman and Costigan
1185 Avenue of the Americas
New York, NY 10036
August 13, 2007

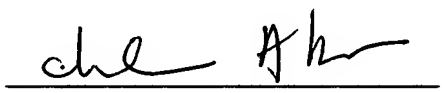
SUPPLEMENTAL RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Supplemental to the response of June 18, 2007, Applicants are submitting an English translation of French priority application No. 97 15230 so the application is entitled to the French filing date of December 3, 1997. This removes the McChargue reference.

Respectfully submitted,
Hedman and Costigan



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CAM:mlp
Enclosures

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Date of Deposit: AUG 13, 2007

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Marie-Louise Pinset

Marie-Louise Pinset

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF TRANSLATION

Honourable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I, JOHN CHARLES McGILLEY, B.A. M.I.T.I., Technical Translator, of c/o Priory Translations Limited, 11, Magdalen Street, Colchester, Essex, England,

hereby state:

THAT I am well acquainted with the French and English languages.

THAT I translated the document identified as French Patent Application No. 97 15230 filed at the National Institute of Industrial Property on 3rd December 1997, from French into English;

THAT the attached English translation is a true and correct translation of French Patent Application No. 97 15230.

to the best of my knowledge and belief; and

THAT all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements are made with the knowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code

JOHN CHARLES McGILLEY

FRENCH REPUBLIC

inpi

NATIONAL INSTITUTE
OF INDUSTRIAL PROPERTY

Patent

of invention

Utility certificate

OFFICIAL COPY

The Director General of the National Institute of Industrial Property certifies that the document annexed hereto is the certified true copy of an application for title of industrial property registered at the Institute.

Drawn up in Paris, 16th July 2007

For the Director General
of the National Institute
of Industrial Property
The Head of the
Patent Department

Martine PLANCHE

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PATENT OF INVENTION , UTILITY CERTIFICATE
Intellectual Property Code, Book VI

REQUEST FOR GRANT
Confirmation of filing by fax ☐

Date of delivery of documents 3rd Dec 1997 National Registration number 97 15230- Postal code of place of filing 75 Date of filing 3rd Dec 1997	**1 NAME AND ADDRESS OF APPLICANT OR REPRESENTATIVE TO WHOM ALL CORRESPONDENCE SHOULD BE ADDRESSED** Monsieur André BOURGOUIN BEAUFOUR IPSEN S.C.A.F. (Service Brevets et Marques) 42 rue du Docteur Blanche 75016 PARIS No. of permanent Power of Attorney: LC 041 Ref of correspondent: RS CAS 258 – DD Telephone: 01 44 30 43 43

2. APPLICATION nature of industrial property right
☒ patent of invention ☐ divisional application
☐ utility certificate ☐ conversion of a European Patent Application ⇒ **initial application**
⇓
☐ patent of invention ☐ utility certificate No. date

Establishment of search report ☐ deferred ☒ immediate
The Applicant, a natural person, requires payment by instalments of the fees ☐ yes ☐ no

Title of the invention (200 characters maximum)
Use of extracts of ginkgo biloba for preparing a medicament intended to ease the withdrawal of individuals who are dependent on the consumption of a substance engendering dependency and/or addiction

3. APPLICANT (s) SIREN No. 3 0 8 1 9 7 1 8 5 APE-NAF code 7 4 1 J Name and forenames (underline surname) or designation SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.) Nationality FRENCH	Legal form Société anonyme
Complete Address 51/53 rue du Docteur Blanche 75016 PARIS	Country FRANCE

4. INVENTOR(S) The inventors are the applicants ☐ yes ☒ no If no, provide a separate designation

5. REDUCTION IN LEVEL OF FEES ☐ requested for the first time ☐ requested prior to filing: attach copy of admission decision

6. DECLARATION OF PRIORITY OR REQUEST FOR BENEFIT FROM THE FILING DATE OF A PREVIOUS APPLICATION

country of origin	number	filing date	nature of application

7. DIVISIONS previous to the present application no. date no. date

8. SIGNATURE OF APPLICANT OR REPRESENTATIVE (name and capacity of signatory - registration no.) [signed] A. BOURGOUIN, Representative	SIGNATURE OF RECEPTION OFFICER	SIGNATURE AFTER REG. OF APPLICATION AT I.N.P.I. [signed]

INPI - NATIONAL INSTITUTE OF INDUSTRIAL PROPERTY
26 bis, rue de Saint Petersbourg, 75800 Paris Cedex 08 Tel: (1) 42.94.52.52. Fax: (1) 42.93.59.30

Patents Administrative Division

DESIGNATION OF INVENTOR
(if the Applicant is not the inventor or the sole inventor)

National Registration No.
9715230

Title of the invention: Use of extracts of Ginkgo biloba for preparing a medicament intended to ease the withdrawal of individuals who are dependent on the consumption of a substance engendering dependency and/or addiction

The Undersigned SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)

Designate(s) as inventor(s) *(specify name, forenames, address and underline surname)*

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75015 PARIS
FRANCE

N.B. *Exceptionally, the inventor's name can be followed by the name of the company to which he belongs (employing company) if this company is different from the company applying or having title.*

Date and signature(s) of applicant(s) or representative
Paris, 15th December 1998

[signed]
A. BOURGOUIN, representative

DOCUMENT INCLUDING AMENDMENTS

PAGE(S) OF THE DESCRIPTION OR OF THE CLAIMS OR SHEET(S) OF DRAWINGS			Amended claim	DATE OF THE CORRESPONDENCE	DATE STAMP OF CORRECTOR
Amended	Cancelled	Added			
20, 22 to 24	25	1/1		12/02/99	30th March 1999 O L

A change introduced in the drawing up of the original claims, except if the former results from the provisions of Article R.612-36 of the Intellectual Property Code, is indicated by the mention "A.C." (amended claims).

Use of extracts of Ginkgo biloba for preparing a medicament intended to ease the withdrawal of individuals who are dependent on the consumption of a substance engendering dependency and/or addiction

The invention relates to the use of extracts of Ginkgo biloba for preparing a medicament intended to ease the withdrawal of individuals who are dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

It is already known that extracts of Ginkgo biloba have an activity in the cardiovascular field (in particular the reduction of platelet adhesion), in the central nervous field (in particular a neuroprotective activity) or in the neurosensory system (in particular retinal protection); cf. for example DeFeudis et al., Ginkgo Biloba Extract (EGb 761), Pharmaceutical Activities and Clinical Applications (Elsevier, Paris, 1991). Their preparation has been the subject of a certain number of patents, of which there can be mentioned the European Patents EP 431 535 and EP 431 536, and the American Patent US 5,389,370.

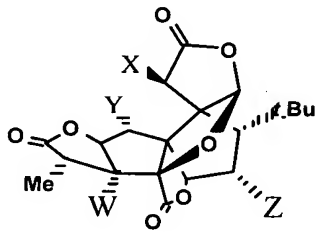
Now the Applicant has just found that certain extracts of Ginkgo biloba also have useful new pharmacological properties, namely easing the withdrawal of subjects addicted to alcohol or drugs, and more generally of subjects dependent on a substance engendering dependency and/or addiction. The Applicant observed that the administration of these extracts resulted in an attenuation of the withdrawal symptoms.

A subject of the invention is therefore the use of these extracts for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

By drugs inducing toxicomania is understood in particular morphine and its derivatives, opium and opiates, cocaine, crack, and more generally all substances, including any medicamentous substance, on which a subject can become dependent.

By extract of Ginkgo biloba is understood at least one of the individual compounds which can be obtained by extraction from the *Ginkgo biloba L* tree, and in particular a flavonoid compound or a terpene such as a ginkgolide or a bilobalide, or also a mixture of the latter. Preferably, the extract used will be such that it contains an effective quantity of ginkgolides. For the uses according to the invention, an extract of type EGb 761 or CP 401 can for example be chosen.

By ginkgolide is understood all the natural ginkgolides obtained from the Ginkgo biloba tree, as well as synthetic ginkgolides and their derivatives (resulting for example from an acetylation or alkoxylation reaction) and pharmaceutically active salts. The ginkgolides used can for example be ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J or ginkgolide M (structures given in the diagram below; these compounds can be isolated from extracts of *Ginkgo biloba* leaves - see *GINKGOLIDES, Chemistry, Biology, Pharmacology and Clinical Perspectives*, published by P. Braquet, J.R. Prous Science Publishers, in particular Volumes 1 (1988) and 2 (1989)). Glycosylated derivatives of ginkgolides or alkoxylated or acetylated derivatives of ginkgolides can also be used. By alkoxylated derivative of ginkgolide is understood a ginkgolide derivative comprising at least one linear or branched alkoxy group, instead of a hydroxy group (these compounds are described in French Patent Application No. FR 88.14392). Similarly, by acetylated derivative of ginkgolide is understood a derivative of ginkgolide comprising at least one acetate group instead of a hydroxy group.



Ginkgolide	W	X	Y	Z
A	OH	OH	H	H
B	OH	OH	OH	H
C	OH	OH	OH	OH
J	OH	OH	H	OH
M	H	OH	OH	OH

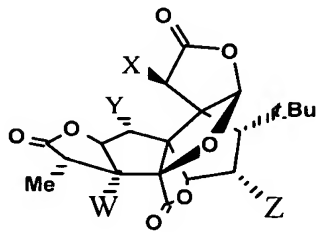
Structure of ginkgolides A, B, C, J and M

By extract of type EGb 761 is understood an extract of a composition substantially identical to that of the standardized extract EGb 761 as defined in particular in the following article: K. Drieu, La presse médicale, **31**, 25 September 1986, supplement devoted to the extract of Ginkgo biloba (EGb 761), 1455-1457; or in the European Patents EP 431 535 and EP 431 536; by extract of type EGb 761 is therefore understood in particular extracts of Ginkgo biloba comprising 20 to 30 % of flavoneglycosides, 2.5 to 4.5 % of ginkgolides A, B, C and J, 2 to 4 % of bilobalide, less than 10 % of proanthocyanidines and less than 10 ppm, and preferably less than 5 ppm, of compounds of alkylphenol type, and in particular extracts of Ginkgo biloba comprising approximately 24 % of flavoneglycosides, 3.1 % of ginkgolides A, B, C and J, 2.9 % of bilobalide, 6.5 % of proanthocyanidines and less than 1 ppm of compounds of alkylphenol type. By extract of type CP 401 is understood extracts such as those which are presented in the Patent US 5,389,370, in particular extracts of Ginkgo biloba containing 5.5 to 8 % of ginkgolides A, B, C and J, 40 to 60 % of flavoneglycosides and 5 to 7 % of bilobalide, and quite particularly extracts containing approximately 7 % of ginkgolides A, B, C and J, 50 % of flavoneglycosides and 6 % of bilobalide.

According to another aspect of the invention, the extract of Ginkgo biloba used will comprise more than 5 % of ginkgolides, and more preferably more than 50 % of ginkgolides.

The invention also relates to the use of a ginkgolide or one of its derivatives or pharmaceutically active salts for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania. Preferably, the ginkgolide used for this aspect of the invention will be ginkgolide A or ginkgolide B.

The invention also relates to the use of a compound of general formula **(I)**



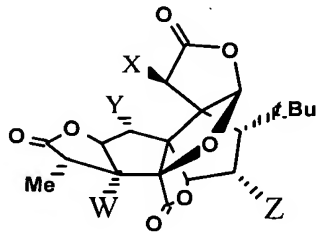
(I)

in which W, X, Y and Z independently represent the H, OH, linear or branched alkoxy or O-G_S, G_S-OH radicals representing a mono- or disaccharide, or one of their derivatives or analogues,

it being understood that at least one of W, X, Y or Z represents an O-G_S radical,

for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, tobacco, amphetamines, drugs inducing toxicomania.

The invention preferably relates to the use of a compound of general formula (**I**)



(**I**)

in which X represents an OH or O-G_S radical, G_S-OH representing a mono- or disaccharide, or one of their derivatives or analogues, and:

- either W represents an OH or O-G_S radical, Y represents H and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents an OH or O-G_S radical;

- or W represents an OH or O-G_S radical, Y represents H and Z represents an OH or O-G_S radical;

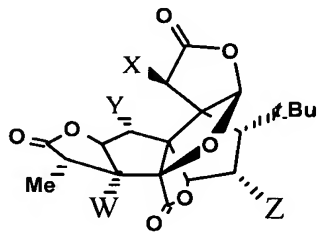
- or W represents H, Y represents an OH or O-G_S radical and Z represents an OH or O-G_S radical;

- or W represents an OH or O-G_S radical, Y represents a linear or branched alkoxy radical and Z represents H;

it being understood that at least one of W, X, Y or Z represents an O-G_S radical,

for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, tobacco, amphetamines, drugs inducing toxicomania.

The invention relates quite particularly to the use of a compound of general formula (**I**)



(**I**)

in which X represents an OH or O-G_S radical, G_S-OH representing a mono- or disaccharide, or one of their derivatives or analogues, and:

- either W represents an OH or O-G_S radical, Y represents H and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents H;

- or W represents an OH or O-G_S radical, Y represents a linear or branched alkoxy radical and Z represents H;

it being understood that at least one of W, X, Y or Z represents an O-G_S radical,

for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, tobacco, amphetamines, drugs inducing toxicomania.

By linear or branched alkoxy radical is understood in the present description an alkoxy radical the linear or branched carbon containing chain of which contains 1 to 6 carbon atoms. By derivative or analogue of mono- or disaccharides is understood compounds such as N-acetylglucosamine, N-acetylalosamine, galactosamine, mannoseamine, N-tosylhydrazone, etc.

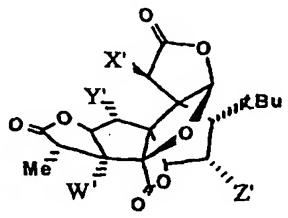
Preferably, O-G_S will be chosen such that G_S-OH belongs to the group comprising abequose, rhamnose, arabinose, ribose, xylose, 2-deoxy-ribose, glucose, galactose, mannose, 2-deoxyglucose, fructose, fucose, N-acetylglucosamine, N-acetylalosamine, galactosamine, mannosamine, saccharose, lactose, maltose, cellobiose and trehalose.

Even more preferentially, O-G_S will be chosen such that G_S-OH belongs to the group comprising glucose and lactose.

The invention therefore also relates to the use of glycosylated derivatives of ginkgolides, more particularly those of ginkgolides A and B, the glycosyl groups suitable for the invention having been described previously.

The different processes for obtaining glycosylated derivatives of ginkgolides or alkoxylated ginkgolides (i.e. those resulting from a glycosylation reaction carried out on at least one of the OH groups of ginkgolides or their alkoxylated derivatives) are described below.

These processes principally comprise a glycosylation stage, which consists of reacting a compound of general formula **(III)** represented below,



(III)

in which W', X', Y' and Z' independently represent an H, OH, linear or branched alkoxy or O-G_x radical, G_x being a protective group of a hydroxy group which can preferably be eliminated in neutral or basic medium, it being understood that at least one of W', X', Y' and Z' represents OH.

with a glycosyl diazirine of general formula **(II)** represented below, the reaction preferably being carried out in THF at temperatures preferably comprised between 20 and 60°C.

(II)

Compound **(II)** is a diazirine derived from a sugar G_p-OH all the hydroxy groups of which except for that carried by the anomeric carbon have been protected, for example

by benzyl or silyl radicals, whilst the hydroxy group in anomeric position and the hydrogen carried by the same carbon atom were substituted by an azi group.

These processes can also comprise one or more stages of protection and/or deprotection of the hydroxy groups. For these stages, a person skilled in the art will use standard methods which are available (Greene, T., Protective Groups in Organic Synthesis 10-86 (John Wiley & Sons 1981)) and will preferably choose protective groups which can be eliminated in basic or neutral medium.

The glycosylation reaction will generally produce, in the case where an excess of glycosyldiazirine is used, a mixture of mono- and diglycosylated derivatives for ginkgolide A or a mixture of mono-, di- and triglycosylated derivatives for ginkgolide B.

In all cases where a mixture of products is obtained, a separation of these products will be carried out according to methods known to a person skilled in the art (in particular, filtration on silica or high performance liquid chromatography with a suitable eluant, or also crystallization or recrystallization from an appropriate solvent).

The sugars or sugar derivatives which can be used for the glycosylation of ginkgolides can be in particular abequose, rhamnose, arabinose, ribose, xylose, 2-deoxy-ribose, glucose, galactose, mannose, 2-deoxyglucose, fructose, fucose, saccharose, lactose, maltose, cellobiose, trehalose, N-acetylglucosamine, N-acetylallosamine, galactosamine, mannosamine, or derivatives of these compounds, in particular the corresponding diazirines, or also N-arylsulphonylhydrazones such as N-tosylhydrazone and their salts.

When the method used is the addition of glycosyl diazirines (general method described in Briner, K., Vasella, A., *Helv. Chim. Acta*, **72**, 1371 (1989)), the following diazirines can in particular be used:

- 1-azi-2,3,4,6-tetra-O-benzyl-1-deoxy-D-glucopyranose or 1-azi-1-deoxy-2,3:5,6-di-O-isopropylidene-D-mannofurannose (syntheses described in Briner, K., Vasella, A., *Helv. Chim. Acta*, **75**(2), 621-637 (1992));
- 1-azi-2,3,4,6-tetra-O-benzyl-1-deoxy-D-galactopyranose (synthesis described in Briner, K., Vasella, A., *Helv. Chim. Acta*, **73**(6), 1764-1779 (1990));
- 1-azi-2,3,4,6-tetra-O-benzyl-1-deoxy-D-mannopyranose (synthesis described in Vasella, A., Witzig, C., Waldraff, C., Uhlmann, P., Briner, K., et al., *Helv. Chim. Acta*, **76**(8), 2847-2875 (1993));
- 2-acetamido-1,5-anhydro-1-azi-3-O-benzyl-4,6-O-benzylidene-1,2-dideoxy-D-allitol (synthesis described in Vasella, A., Dhar, P., Witzig, C., *Helv. Chim. Acta*,

76(4) 1767-1778 (1993) and Linden, A., Vasella, A., Witzig, C., *Helv. Chim. Acta*, **75**(5), 1572-1577 (1992));

- 1,5-anhydro-1-azi-2-deoxy-3,4,6-tri-O-pivaloyl-D-glucitol (synthesis described in Takahashi, Y., Vasella, A., *Helv. Chim. Acta*, **75**(5), 1563-1571 (1992));
- 1,5-anhydro-1-azi-2,3,4,6-tetra-O-pivaloyl-D-glucitol or 2-acetamido-1,5-anhydro-1-azi-3-O-benzyl-4,6-O-benzylidene-1,2-dideoxy-D-glucitol (synthesis described in Vasella, A., Witzig, C., Waldraff, C., Uhlmann, P., Briner, K., et al., *Helv. Chim. Acta*, **76**(8), 2847-2875 (1993));
- 1,5-anhydro-1-azi-2,3-di-O-benzyl-4,6-O-benzylidene-D-mannitol (synthesis described in Uhlmann, P., Briner, K., et al., *Helv. Chim. Acta*, **76**(8), 2847-2875 (1993));
- 1,5-anhydro-1-azi-2,3-di-O-benzyl-4,6-O-(4-methoxybenzylidene)-D-glucitol (synthesis described in Vasella, A., Witzig, C., Waldraff, C., Uhlmann, P., Briner, K., et al., *Helv. Chim. Acta*, **76**(8), 2847-2875 (1993));
- 2-acetamido-1,5-anhydro-1-azi-3,4,6-tri-O-benzyl-2-deoxy-D-glucitol (synthesis described in Vasella, A., Witzig, C., Waldraff, C., Uhlmann, P., Briner, K., et al., *Helv. Chim. Acta*, **76**(8), 2847-2875 (1993));
- 1-azi-1-deoxy-2,3:4,6-di-isopropylidene-D-glucopyranose (synthesis described in Uhlmann, P., Hart, E., Naughton, A.B., Vasella, A., *Helv. Chim. Acta*, **77**(8), 2335-2340 (1994));
- (Z)-N'-2,3,5-tri-O-benzyl-D-(ribofuranosylidene)toluene-4-sulphonohydrazide or (Z)-N'-2,3,5-tri-O-benzyl-D-(arabinofuranosylidene)toluene-4-sulphonohydrazide (synthesis described in Mangholz, S.E., Vasella, A., *Helv. Chim. Acta*, **78**(4), 1020-1035 (1995));
- 1-azi-2,3,6-tri-O-benzyl-4-O[2,3,4,6-tetra-O-benzyl-D-galactopyranosyl]1-deoxy-D-glucopyranose (synthesis according to Briner, K., Vasella, A., *Helv. Chim. Acta*, **72**, 1371 (1989)).

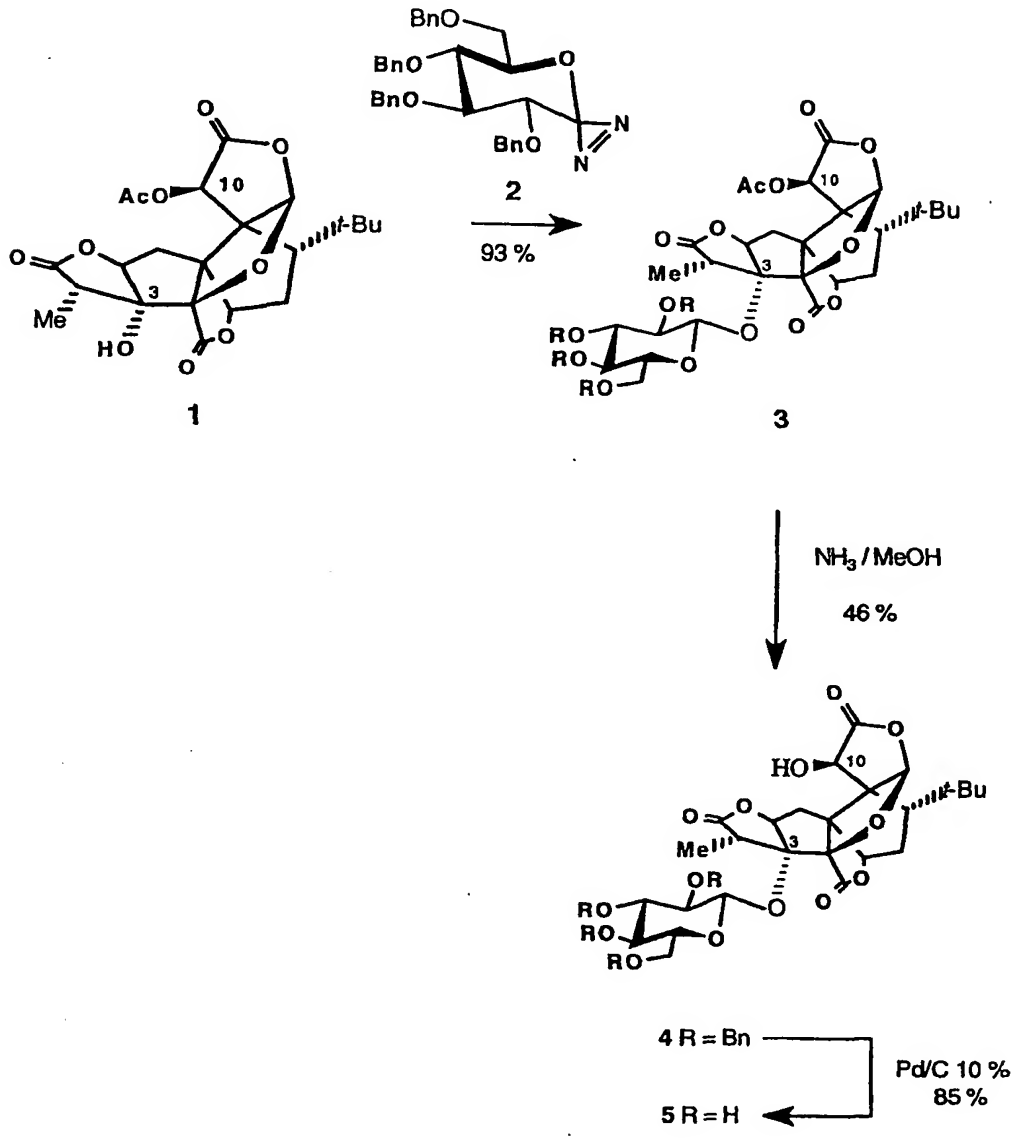
A person skilled in the art will of course be able to choose other compounds of the same type should it be judged necessary.

The solvents which can be used for the glycosylation reaction are 1,4-dioxane, THF, toluene, methylene chloride or 1,2-dichloroethane. Preferably, THF will be used.

The reaction conditions can be thermal or photolytic conditions. For thermal conditions the operation will be carried out at temperatures preferably comprised between 25 and 60°. For photolytic conditions, the operation will be carried out at a low temperature, typically between –80°C and –60°C, generally with THF as the solvent. For the photolysis, a high pressure mercury lamp *Philips HPK-125* can for example be used.

Typically, irradiation will take place over a period of approximately one hour, or more if necessary.

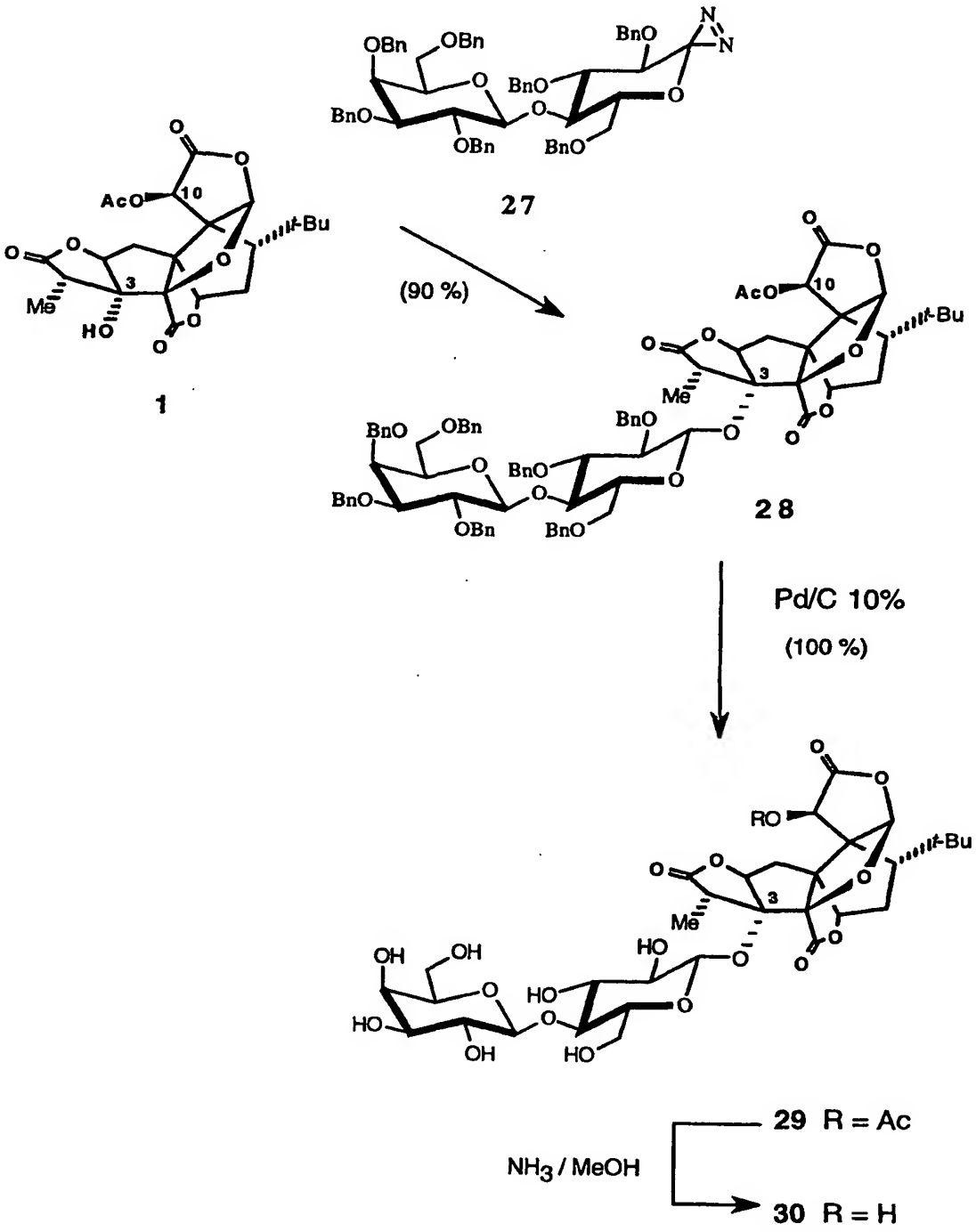
For the monoglucosylated derivatives of ginkgolide A, a possible synthesis route is as follows:



The 10-O-acetyl-ginkgolide A (**1**) (prepared from ginkgolide A which is reacted for 25 hours at ambient temperature with acetic anhydride in excess in pyridine) is treated for one hour 30 minutes at 30°C with approximately 1.3 equivalent of glucosyl diazirine **2**, the reaction being carried out in THF. After evaporation and crystallization, **3** is then obtained which is treated with NH_3 in MeOH in order to produce the deacetylated product **A**. The debenzylation **4** is then carried out in a standard fashion y hydrogenation with 10% Pd/C in MeOH. 3-O-(β-D-glucopyranosyl)ginkgolide A (**5**) is then obtained. It will be noted that the debenzylation and deacetylation stages can be reversed.

In the same way as the synthesis of the monoglucosylated derivatives of ginkgolide A can be carried out, that of the monoglucosylated derivatives of ginkgolide A can be carried out by using other glycosyl diazirines such as those described previously or by carrying out the glycosylation reaction under standard conditions (described in the literature).

By way of example, 3-O-[(4-O-β-D-galactopyranosyl]-β-D-glucopyranosyl] ginkgolide A can be obtained by the following route

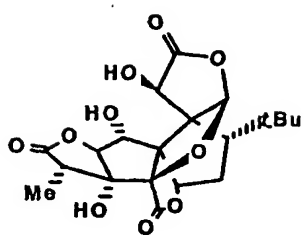


The ginkgolide A (**1**) is treated with a solution of diazirine **27** in THF for one hour. Then **28** is obtained with a yield of 90 %. **28** is debenzylated by hydrogenation in the presence of 10 % Pd/C in order to produce **29**. Finally, **29** can be deacetylated by

standard methods (for example NH_3/MeOH) in order to produce 3-O-[(4-O-β-D-galactopyranosyl)-β-D-glucopyranosyl] ginkgolide A (**30**). As previously, the last two stages can of course be reversed.

If one wishes to obtain the diglycosylated derivative of ginkgolide A, it is sufficient to start with ginkgolide A and not 10-O-acetyl- ginkgolide A (**1**) and to use an excess of glycosyl diazirine or glycosylating reagent if another glycolsylation reaction is chosen.

A possible synthesis route for derivatives of ginkgolide B according to the invention is as follows:



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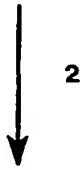

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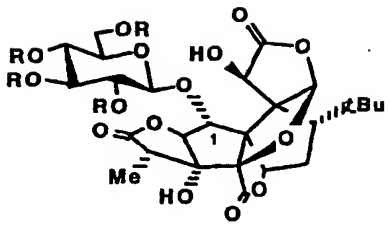
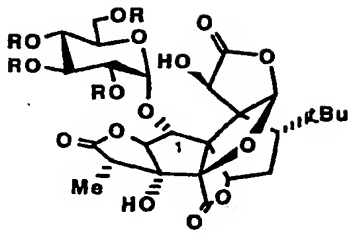
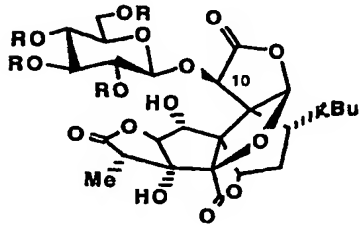
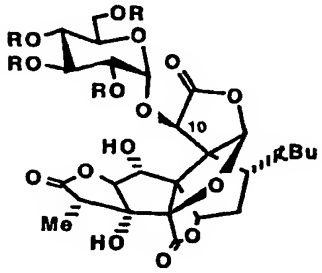




7 R = Bn ⟶ 19 R = H 8 R = Bn ⟶ 20 R = H



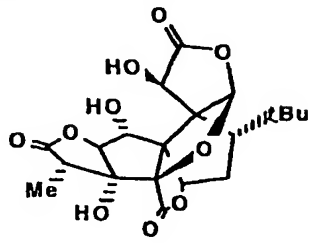


9 R = Bn ⟶ 21 R = H 10 R = Bn ⟶ 22 R = H

In order to obtain monoglucosylated derivatives of ginkgolide B (**6**), photolytic conditions will preferably be chosen for the glycosylation reaction, by using from approximately 1 to 1.35 equivalent of glucosyl diazirine **2** per equivalent of ginkgolide. The debenzylation of the monoglucosylated derivatives **7, 8, 9** and **10** in order to produce compounds **19, 20, 21** and **22** respectively is carried out as described previously for the debenzylation of compound **4**.

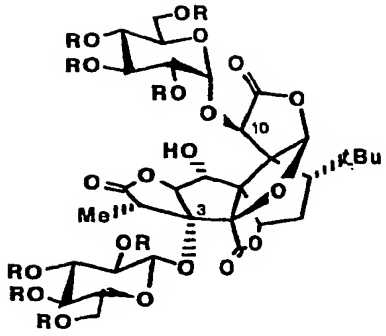
The monoglucosylated derivatives of ginkgolide B are obtained in the same way by starting with glycosyl diazirines other than **2**, or by starting with another glycosylating reagent and by using a glycosylation reaction such as those described in the literature. The deprotection stages following the glycosylation reaction remain the same.

If one wishes to obtain diglucosylated derivatives of ginkgolide B, the following synthesis route can for example be used:



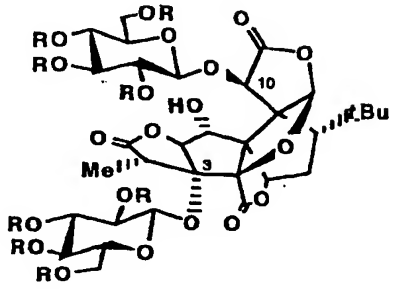
6

2 equivalents of **2**



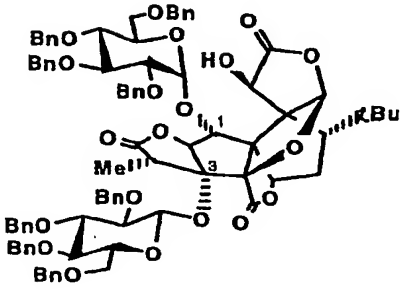
11 R = Bn ⟶ **23** R = H

⊕



12 R = Bn ⟶ **24** R = H

⊕



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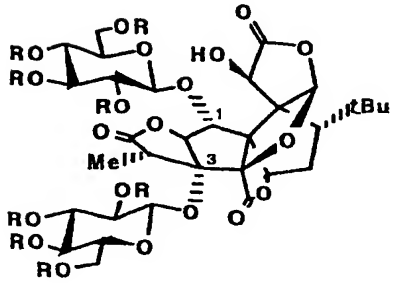
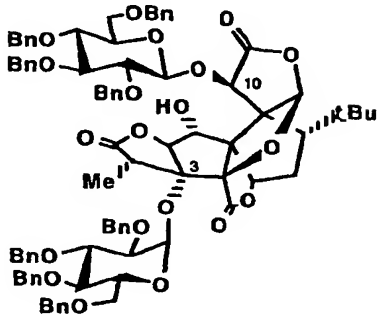


14 R = Bn ⟶ **25** R = H

⊕

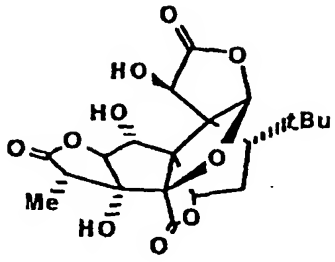


15

In order to obtain diglycosylated derivatives of ginkgolide B (**6**), **6** is reacted for 1 hour at 30°C in THF with 1 equivalent of glucosyl diazirine **2**, then another 1 equivalent of glucosyl diazirine **2** is added and the medium is left to react under the same conditions for 17 hours. A mixture of diglycosylated derivatives **11, 12, 13, 14** and **15** is then obtained. These derivatives can then be debenzylated by hydrogenation with 10 % Pd/C in MeOH.

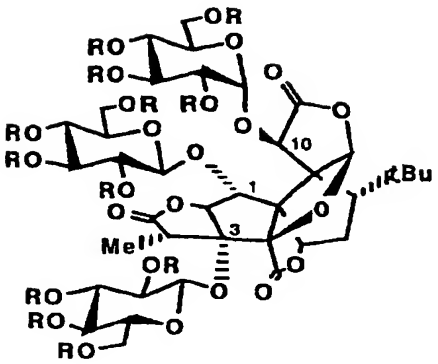
The diglycosylated derivatives of ginkgolide B are obtained in the same way starting from glycosyl diazirines other than **2**, or by starting with another glycosylating reagent and by using a glycosylation reaction such as those described in the literature. The deprotection stages following the glycosylation reaction remain the same.

In order to obtain triglucosylated derivatives of ginkgolide B, the following synthesis route will be used:



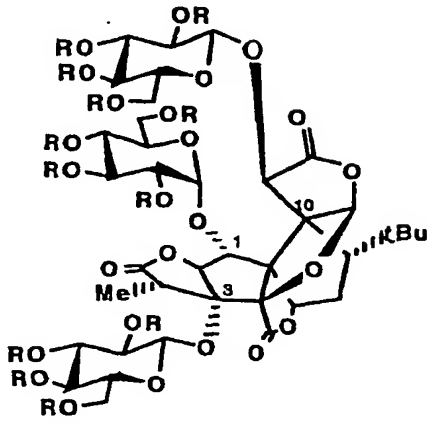
6

3.5 equivalents of **2**



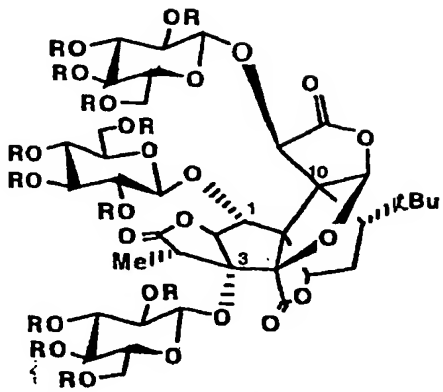
16 R = Bn

⊕



17 R = Bn

⊕



18 R = Bn ⟶ **26** R = H

The triglucosylated derivatives of ginkgolide B (**6**) are obtained by the reaction of **6** with at least 3.5 equivalents of glucosyl diazirine **2** in THF at 25°C, the addition of **2** being carried out in 2 goes separated by an interval of 24 hours for example. The medium is left to react for approximately one day and 1,3,10-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)ginkgolide B (**18**) is obtained in the majority. 1,3-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-10-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl) ginkgolide B (**16**) and 1-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-3,10-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)ginkgolide B (**17**) are also obtained. **18** can then be debenzylated by hydrogenation with 10 % Pd/C in MeOH and 1,3,10-O-(β-D-glucopyranosyl)ginkgolide B (**26**) is then obtained. By the same method **16** and **17** can be debenzylated in order to obtain the corresponding debenzylated derivatives.

The triglucosylated derivatives of ginkgolide B are obtained in the same way starting from glycosyl diazirines other than **2**, or by starting with another glycosylating reagent and by using a glycosylation reaction such as those described in the literature. The deprotection stages following the glycosylation reaction remain the same.

Ginkgolide C can be glycosylated in a similar fashion to that used for ginkgolides A or B. A person skilled in the art will choose the stoichiometry in glycosyl diazirine or in glycosylating reagent as a function of the degree of glycosylation desired (mono-, di-, tri or tetraglycosylated derivatives).

In the same way, the processes described previously can be applied to ginkgolides J and M in order to produce the glycosylated derivatives of the latter, or to alkoxylated derivatives of ginkgolides in order to produce the corresponding glycosylated compounds.

The pharmaceutical compositions comprising a compound of the invention can be in the form of solids, for example powders, granules, tablets, gelatin capsules, liposomes or suppositories. Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax.

The pharmaceutical compositions containing a compound of the invention can also be presented in liquid form, for example, solutions, emulsions, suspensions or syrups. Appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols, as well as their mixtures, in varying proportions, in water.

The administration of a medicament according to the invention can be carried out by topical, oral, parenteral route, by injection (intramuscular, sub-cutaneous, intravenous, etc.), etc.

The administration dose envisaged for a medicament according to the invention is comprised between 0.1 mg and 10 g according to the type of substance on which the subject to be treated is dependent.

Unless they are defined differently, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. Similarly, all publications, patent applications, all patents and all other references mentioned here are incorporated by way of reference.

Pharmacological study of the products of the invention:

1. Study of the effects of extracts of Ginkgo biloba on alcohol dependency:

Two studies were carried out: one relates to the effects of EGb 761, the other to the effects of another extract of Ginkgo biloba, CP 401, which does not contain bilobalide but twice as much ginkgolides as EGb 761 (6 %).

1) Rats are treated for 15 days with alcohol (they are administered 10 % ethanol in their drinking water for the first week and then 12.5 % ethanol). They are given 50 or 100 mg/kg of EGb 761 per day by oral route (gavage) for the 5 days before the absorption of alcohol is stopped (from the 11th day) and the 3 days after it is stopped.

The behavioural symptoms were evaluated for 3 days after the absorption of alcohol is stopped in three groups of rats (n=6): the control group having received only alcohol, one group having received alcohol and treatment with 50 mg/kg of EGb 761 and another group having received alcohol and treatment with 100 mg/kg of EGb 761, the treatments with EGb 761 having been administered under the conditions described above. The results of these tests are shown in table **(I)** which can be found in appendix I.

In the animals which received EGb 761, it can be observed that the withdrawal symptoms (7 criteria) are reduced in a dose-dependent manner and that the animals also have reduced motor hyperactivity.

2) Rats are treated for 15 days with alcohol (they are given 10 % ethanol in their drinking water for the first week and then 12.5 % ethanol). They are administered 50 mg/kg of CP 401 extract per day by oral route (gavage) for the 5 days before the absorption of alcohol is stopped (from the 11th day) and the 3 days after it is stopped.

The behavioural symptoms were evaluated for the 3 days after the absorption of alcohol was stopped in three groups of rats (n=6): the control group only having received alcohol and the other group having received alcohol and treatment with 50 mg/kg of CP 401 extract administered under the conditions described above. The results of these tests are shown in table **(II)** which can be found in appendix I.

It is observed that the animals which received the CP 401 extract show a reduction in the symptoms linked with withdrawal compared with the intoxicated control animals.

2. Study of the effects of Ginkgo biloba extracts on sensitization to amphetamine:

An injection of amphetamine (0.5 mg/kg IP) provokes motor hyperactivity in the rat (measured by actimetry). Administration eight times, every other day, of the same dose of amphetamine results in a progressive increase in locomotive activity: this phenomenon is called "sensitization".

For 8 days before the administration of amphetamine and throughout this administration, rats (n=8) subjected to the administration of amphetamine as described above were subjected to treatment by oral route with a dose of EGb 761 of 100 mg/kg per day or with a dose of 5 mg/kg per day of ginkgolide A .

Actimetry measurements were carried out for 1 hour after the administration of the amphetamine on the 9th (first day on which amphetamine was administered), 13th, 17th, 21st and 25th day. The results of these tests are shown in Figure **A** which can be found in appendix II.

It is observed that behavioural sensitization to amphetamine is reduced in the animals which received 5 mg/kg per day of ginkgolide A. An enhanced and quite significant effect is observed with EGb 761 at 100 mg/kg per day.

3. Study of the effects of Ginkgo biloba extract EGb 761 on morphine withdrawal syndrome:

Rats are treated every 8 hours (3 times per day) for 10 days with a dose of morphine by sub-cutaneous route resulting in motor hyperactivity (measured by actimetry). On the 11th day, they are administered naloxone (3 mg/kg IP) and the withdrawal signs are observed for 60 minutes: a series of behavioural signs is quantified, a series measured (hypothermia, weight loss) or a series graded (scale with 4 levels).

Two groups of 8 rats are treated with EGb 761 (50 or 100 mg/kg per day) for 4 days before the administration of naloxone and 2 hours before it. A group of intoxicated control rats only receives injections of morphine before the naloxone and an absolute control group only receives naloxone.

Statistical analysis of the batches is carried out using the following tests: parametric Anova, Barlett's test to check the homogeneity of variances and Dunnett's test for multiple comparisons.

Claims

1. Use of a Ginkgo biloba extract for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

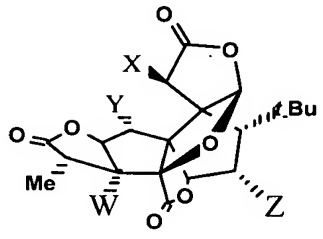
2. Use according to claim 1, characterized in that the Ginkgo biloba extract is an extract of type EGb 761.

3. Use according to claim 1, characterized in that the Ginkgo biloba extract is an extract of type CP 401.

4. Use according to claim 1, characterized in that the Ginkgo biloba extract contains at least 5 % of ginkgolides.

5. Use according to claim 4, characterized in that the Ginkgo biloba extract contains at least 50 % of ginkgolides.

6. Use of a compound of general formula **(I)**



(I)

in which W, X, Y and Z independently represent the H, OH, linear or branched alkoxy or O-G_S radicals, G_S-OH representing a mono- or a disaccharide, or one of their derivatives or analogues,

it being understood that at least one of W, X, Y or Z represents an O-G_S radical,

for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

7. Use according to claim 6, characterized in that:

- either W represents an OH or O-G_S radical, Y represents H and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents an OH or O-G_S radical;

- or W represents an OH or O-G_S radical, Y represents H and Z represents an OH or O-G_S radical;

- or W represents H, Y represents an OH or O-G_S radical and Z represents an OH or O-G_S radical;

- or W represents an OH or O-G_S radical, Y represents a linear or branched alkoxy radical and Z represents H;

it being understood that at least one of W, X, Y or Z represents an O-G_S radical.

8. Use according to claim 6 or 7, characterized in that:

- either W represents an OH or O-G_S radical, Y represents H and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents H;

- or W represents an OH or O-G_S radical, Y represents a linear or branched alkoxy radical and Z represents H;

it being understood that at least one of W, X, Y or Z represents an O-G_S radical.

9. Use of a ginkgolide or one of its derivatives, or pharmaceutically active salts for preparing a medicament medium intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering habituation and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

10. Use according to claim 9, characterized in that the ginkgolide is ginkgolide A or ginkgolide B.

APPENDIX I

Treatment (mg/kg)	TRE	SNO	CHA	TWI	MOT	ESC	JUM
none	7	17	15	12	11	6	5
EGb 761 (50)	5	9	8	6	6	3	2
EGb 761 (100)	0	5	4	2	3	0	1

Table I – Influence of treatment with substance EGb 761 on the number of observations of each symptom of abstinence at 24 hours after withdrawal

Treatment (mg/kg)	TRE	SNO	CHA	TWI	MOT	ESC	JUM
none	6	19	12	15	9	6	6
CP 401 (50)	4	11	6	7	5	4	3

Table II – Influence of treatment with substance CP 401 on the number of observations of each symptom of abstinence at 24 hours after withdrawal

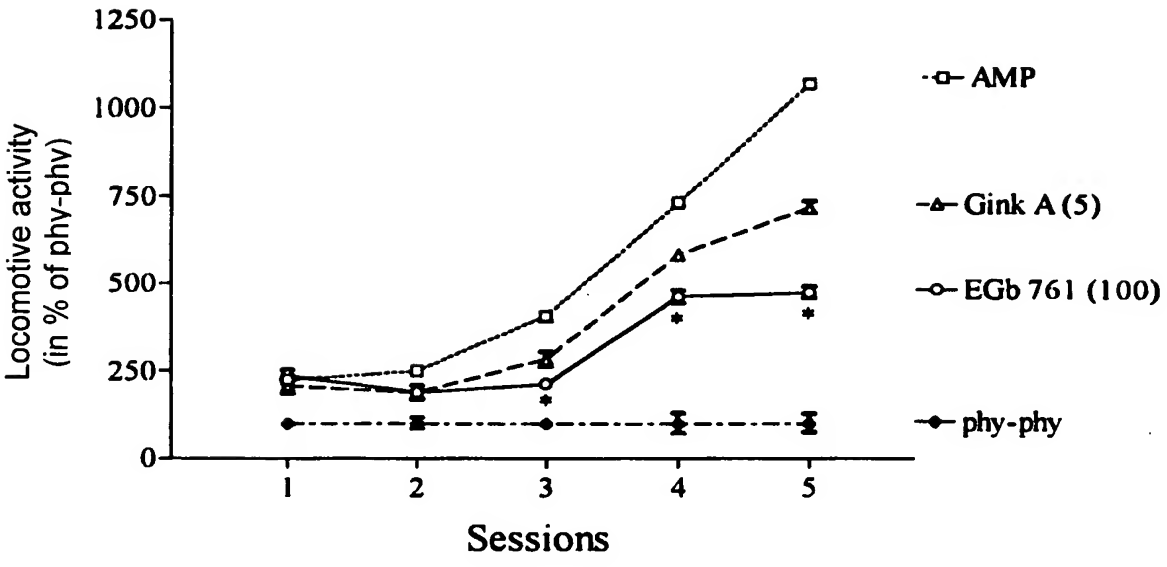
Legend common to Tables I and II

TRE: trembling in body
SNO: snorting
CHA: chattering of teeth
TWI: twitching of ears
MOT: motor activity
ESC: attempted escapes
JUM: jumps

The symptoms are graded from 0 to 3 according to their intensity (0 = slight; 3 = very pronounced).

APPENDIX II

Effect of substances EGb 761 and Ginkgolide A on sensitization to amphetamine



(*) significantly different from amphetamine group ($p<0.05$)

Figure A

2) Rats are treated for 15 days with alcohol (they are given 10 % ethanol in their drinking water for the first week and then 12.5 % ethanol). They are administered 50 mg/kg of CP 401 extract per day by oral route (gavage) for the 5 days before the absorption of alcohol is stopped (from the 11th day) and the 3 days after it is stopped.

The behavioural symptoms were evaluated for the 3 days after the absorption of alcohol was stopped in three groups of rats (n=6): the control group only having received alcohol and the other group having received alcohol and treatment with 50 mg/kg of CP 401 extract administered under the conditions described above. The results of these tests are shown in table **(II)** which can be found in appendix I.

It is observed that the animals which received the CP 401 extract show a reduction in the symptoms linked with withdrawal compared with the intoxicated control animals.

2. Study of the effects of Ginkgo biloba extracts on sensitization to amphetamine:

An injection of amphetamine (0.5 mg/kg IP) provokes motor hyperactivity in the rat (measured by actimetry). Administration eight times, every other day, of the same dose of amphetamine results in a progressive increase in locomotive activity: this phenomenon is called "sensitization".

For 8 days before the administration of amphetamine and throughout this administration, rats (n=8) subjected to the administration of amphetamine as described above were subjected to treatment by oral route with a dose of EGb 761 of 100 mg/kg per day or of a dose of 5 mg/kg per day of ginkgolide A .

Actimetry measurements were carried out for 1 hour after the administration of the amphetamine on the 9th (first day on which amphetamine was administered), 13th, 17th, 21st and 25th day. The results of these tests are shown in Figure **A** which can be found on sheet1/1.

It is observed that behavioural sensitization to amphetamine is reduced in the animals which received 5 mg/kg per day of ginkgolide A. An enhanced and quite significant effect is observed with EGb 761 at 100 mg/kg per day.

APPENDIX I

Treatment (mg/kg)	TRE	SNO	CHA	TWI	MOT	ESC	JUM
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EGb 761 (50)	5	9	8	6	6	3	2
EGb 761 (100)	0	5	4	2	3	0	1

Table I – Influence of treatment with substance EGb 761 on the number of observations of each symptom of abstinence at 24 hours after withdrawal

Treatment (mg/kg)	TRE	SNO	CHA	TWI	MOT	ESC	JUM
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Table II – Influence of treatment with substance CP 401 on the number of observations of each symptom of abstinence at 24 hours after withdrawal

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The symptoms are graded from 0 to 3 according to their intensity (0 = slight; 3 = very pronounced).

Claims

1. Use of a Ginkgo biloba extract for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

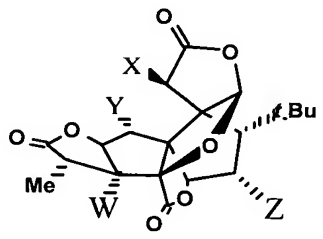
2. Use according to claim 1, characterized in that the Ginkgo biloba extract is an extract of type EGb 761.

3. Use according to claim 1, characterized in that the Ginkgo biloba extract is an extract of type CP 401.

4. Use according to claim 1, characterized in that the Ginkgo biloba extract contains at least 5 % of ginkgolides.

5. Use according to claim 4, characterized in that the Ginkgo biloba extract contains at least 50 % of ginkgolides.

6. Use of a compound of general formula **(I)**



(I)

in which W, X, Y and Z independently represent the H, OH, linear or branched alkoxy or O-G_S radicals, G_S-OH representing a mono- or a disaccharide, or one of their derivatives or analogues,

it being understood that at least one of W, X, Y or Z represents an O-G_S radical,

for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering dependency and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

7. Use according to claim 6, characterized in that:

- either W represents an OH or O-G_S radical, Y represents H and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents an OH or O-G_S radical;

- or W represents an OH or O-G_S radical, Y represents H and Z represents an OH or O-G_S radical;

- or W represents H, Y represents an OH or O-G_S radical and Z represents an OH or O-G_S radical;

- or W represents an OH or O-G_S radical, Y represents a linear or branched alkoxy radical and Z represents H;

it being understood that at least one of W, X, Y or Z represents an O-G_S radical.

8. Use according to claim 6 or 7, characterized in that:

- either W represents an OH or O-G_S radical, Y represents H and Z represents H;

- or W represents an OH or O-G_S radical, Y represents an OH or O-G_S radical and Z represents H;

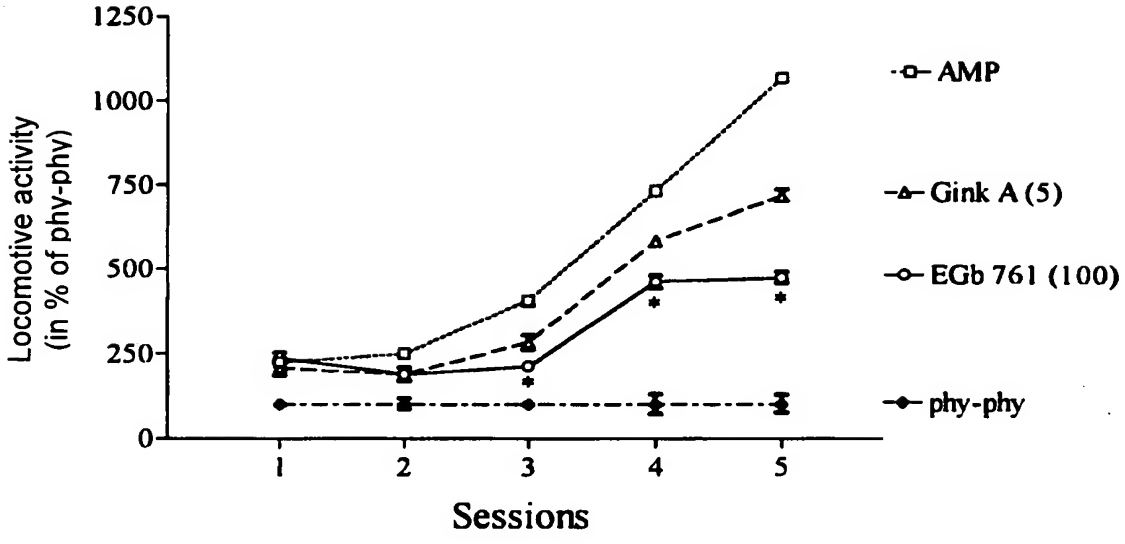
- or W represents an OH or O-G_S radical, Y represents a linear or branched alkoxy radical and Z represents H;

it being understood that at least one of W, X, Y or Z represents an O-G_S radical.

9. Use of a ginkgolide or one of its derivatives, or pharmaceutically active salts for preparing a medicament intended to ease the withdrawal of individuals dependent on the consumption of a substance engendering habituation and/or addiction, such as in particular alcohol, amphetamines, tobacco, drugs inducing toxicomania.

10. Use according to claim 9, characterized in that the ginkgolide is ginkgolide A or ginkgolide B.

Effect of substances EGb 761 and Ginkgolide A on sensitization to amphetamine



(*) significantly different from amphetamine group ($p<0.05$)

Figure A